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Luders, E ; Narr, K L ; Thompson, P M ; Rex, D E ; Jäncke, L ; Toga, A W

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# Hemispheric Asymmetries in Cortical Thickness

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Using magnetic resonance imaging and computational cortical pattern matching methods, we analyzed hemispheric differences in regional gray matter thickness across the lateral and medial cortices in young, healthy adults ( $n = 60$ ). In addition, we investigated the influence of gender on the degree of thickness asymmetry. Results revealed global and regionally specific differences between the two hemispheres, with generally thicker cortex in the left hemisphere. Regions with significant leftward asymmetry were identified in the precentral gyrus, middle frontal, anterior temporal and superior parietal lobes, while rightward asymmetry was prominent in the inferior posterior temporal lobe and inferior frontal lobe. On the medial surface, significant rightward asymmetries were observed in posterior regions, while significant leftward asymmetries were evident from the vicinity of the paracentral gyrus extending anteriorly. Asymmetry profiles were similar in both sexes, but hemispheric differences appeared slightly pronounced in males compared with females, albeit a few regions also indicated greater asymmetry in females compared with males. Hemispheric differences in the thickness of the cortex might be related to hemisphere-specific functional specializations that are possibly related to behavioral asymmetries.

**Keywords:** cortex, gender, gray, lateralization, sex difference

## Introduction

The brain exhibits macroscopic asymmetries (e.g. in volume, fissurization), microscopic asymmetries (e.g. in cytoarchitecture and dendritic arborization) and neurochemical asymmetries, such as dopaminergic and noradrenergic sensitivity (Toga and Thompson, 2003). Moreover, both regions-of-interest (ROI) studies and automated whole-brain analysis techniques have revealed anatomic findings that correspond with functional lateralization (Jancke and Steinmetz, 2003). For example, with respect to the concentration of gray matter (GM), researchers have observed leftward asymmetries in regions involved in language processing (Niznikiewicz *et al.*, 2000; Good *et al.*, 2001; Watkins *et al.*, 2001), which agrees with the documented left-hemispheric dominance for language (Price, 2000).

Recent advances in computerized image analysis methods now allow the automated analyses of thickness across the cortex (Fischl and Dale, 2000; Jones *et al.*, 2000; Miller *et al.*, 2000; Kabani *et al.*, 2001; Kruggel *et al.*, 2003; Lohmann *et al.*, 2003; Yezzi and Prince, 2003; Lerch *et al.*, 2004; Memoli *et al.*, 2004; Lerch and Evans, 2005). The investigation of cortical thickness may provide further insights into hemispheric differences in brain morphology and how they may relate to functional asymmetries. However, statistical evaluations of thickness asymmetries in the human brain are rare. Thus, our goal was to examine hemispheric differences in regional thickness in

a large MR data set of healthy, age-matched subjects (30 men, 30 women). We set out to generate spatially detailed maps indexing thickness asymmetry across the lateral and medial cortices with sub-millimeter resolution. Since cortical thickness may reflect microstructural factors (Kruggel *et al.*, 2003; Eickhoff *et al.*, 2004), we expected that asymmetry effects would parallel known functional asymmetries in regions predominantly related to language and hand-specific motor functions. As a final goal, we aimed to investigate whether thickness asymmetries are significantly different in men and women, given that greater structural asymmetries and functional lateralization have been frequently documented in males.

## Materials and Methods

### Subjects and MRI Acquisition

Cortical thickness was examined in a well-matched sample of healthy men ( $n = 30$ ,  $25.5 \pm 4.7$  years) and women ( $n = 30$ ,  $24.3 \pm 4.4$  years), who gave informed consent according to institutional guidelines (Ethics Committee of the University of Magdeburg). All subjects were right-handers with handedness determined by referring to self-reports of hand preference. High-resolution SPGR T1-weighted magnetic resonance images ( $256 \times 256 \times 124$  matrix,  $0.98 \times 0.98 \times 1.5$  mm voxel size) were obtained on a 1.5 T scanner (General Electric, Waukesha, WI).

### Image Processing

Image volumes passed through a number of preprocessing steps (Thompson *et al.*, 2004) using mostly automated procedures implemented in the LONI (Laboratory of Neuro Imaging) Pipeline Processing Environment (Rex *et al.*, 2003). First, we created an intracranial mask of the brain using a brain surface extraction algorithm tool (BSE) that is based on a combination of non-linear smoothing, edge finding and morphologic processing (Shattuck and Leahy, 2002). Any small errors in the masks were corrected manually to separate intracranial regions from surrounding extracranial tissue. Brain masks and anatomical images were corrected for head alignment and individual differences in brain size by using an automatic 12-parameter linear registration (Woods *et al.*, 1998) to transform each brain volume into the target space and dimensions of the ICBM-452 average brain (Rex *et al.*, 2003). Of note, because aligning image volumes to an asymmetric template might artificially introduce or increase asymmetry in our original data (Good *et al.*, 2001; Watkins *et al.*, 2001), both hemispheres of our image volumes (left and right) were aligned to the left hemisphere of the ICBM-452 brain. Using the normalized brain masks, all extracerebral tissues were removed from the normalized image volumes. After applying radiofrequency (RF) bias field corrections to eliminate intensity drifts due to magnetic field inhomogeneities (Shattuck *et al.*, 2001), each image volume was segmented into different tissue types by classifying voxels as most representative of GM, white matter (WM), cerebrospinal fluid (CSF) or a background class (Shattuck *et al.*, 2001). The procedure fits a mixture of Gaussian distributions to the intensities in each image, before assigning each voxel to the class with the highest probability based on their signal intensity values. Tissue classified brain volumes were split into the two hemispheres and resampled using trilinear interpolation to 0.33 mm isotropic voxels to improve the

spatial resolution and precision of subsequent thickness measurements (Thompson *et al.*, 2005).

### **Cortical Thickness Measurement**

Cortical thickness — defined as the 3D distance (in mm) between inner GM-WM border and the closest point on the outer surface (CSF/GM border) — was calculated using the Eikonal fire equation (Sapiro, 2001; Memoli *et al.*, 2004; Thompson *et al.*, 2004, 2005) applied to voxels that were classified as GM. More specifically, we identified the GM-WM interface as the set of voxels classified as GM that have at least one neighboring WM voxel, setting the distance values for this layer of voxels to zero. In order to estimate cortical thickness, we coded successive layers of voxels by assigning them a value equal to the closest 3D distance to the GM-WM interface. That is, in series of subsequent passes over the image (from inside to outside), layers that are adjacent to the voxel layer coded in the last step will be processed and assigned a distance value. As such, the coding of distance values takes place from the inner surface of the cortex outwards, so the thickness field increases in a direction that is approximately perpendicular to the GM-WM interface. Essentially, the process computes the shortest distance from a given GM voxel to the nearest WM voxel, avoiding solutions where this line would pass through CSF. Avoidance of WM voxels is not necessary since the existence of a shortcut across WM automatically implies that the shortest path has not yet been found (Thompson *et al.*, 2005). Because the thickness is coded in the 3D image, there is not a problem related to the orientation of the cortical mantle, as the coding of thickness values will proceed sequentially in an orientation that is local orthogonal to the GM-WM interface, even if that is not parallel to the scalp.

With respect to establishing thickness measures along sidewalls of the sulci, the current method will code GM voxels on either side of the sulcus with increasing distance values in a series of passes over the data, until they meet in the middle. This method suffers from ambiguity when two GM surfaces meet without being separated by a CSF intensity voxel, due to partial voluming. In this case, the method must effectively assume that the boundary lies at the point that produces equal thickness for both of the opposing GM surfaces. However, this has virtually no impact on the results; for example assigning both surfaces 4 mm is effectively indistinguishable from assigning 3 mm and the other 5 mm (which might be the true values) due to the subsequent smoothing (Thompson *et al.*, 2005).

### **Smoothing Procedure**

Finally, thickness data was smoothed by defining a local smoothing kernel of radius 15 mm at each vertex on the cortical surface model. That is, the mean distance code was computed for all voxels in the local maxima field that lie under the 15 mm kernel, disregarding voxels that are not in the local maxima field. Consequently, thickness values on each vertex represent the average thickness from the surrounding area, computed over a small region in the 3D volume onto the extracted cortical surface. Hence, thickness obtained from sulcal depths also contributes to the regional average thickness. Inevitably, through the smoothing procedure thickness values of neighbouring areas are 'averaged' together, resulting into a loss of information which, in some cases, can also bias regional outcomes in average maps (e.g. pre- and post-central gyrus appear to have same thickness values, although true thickness values in pre-central regions are actually higher than in post-central regions). This notwithstanding, smoothing is necessary in order to increase the signal-to-noise ratio and to reduce slight differences in spatial homology between hemispheres. Moreover, smoothing is advantageous for maintaining statistical power by increasing the chance to detect group- or hemisphere-specific effects. Notably, although smoothing might bias thickness data to some extent, the bias is introduced equally over subjects and hemispheres. Thus, thickness asymmetry results should be unaffected by smoothing artifacts.

### **Cortical Pattern Matching**

Cortical pattern matching methods (Thompson *et al.*, 2004) were used to spatially relate homologous regions of cortex across hemispheres, as well as within hemispheres across subjects, in order to facilitate the inter-hemispheric and inter-individual comparison of cortical thickness in equivalent surface locations. For that purpose, we created 3D cortical

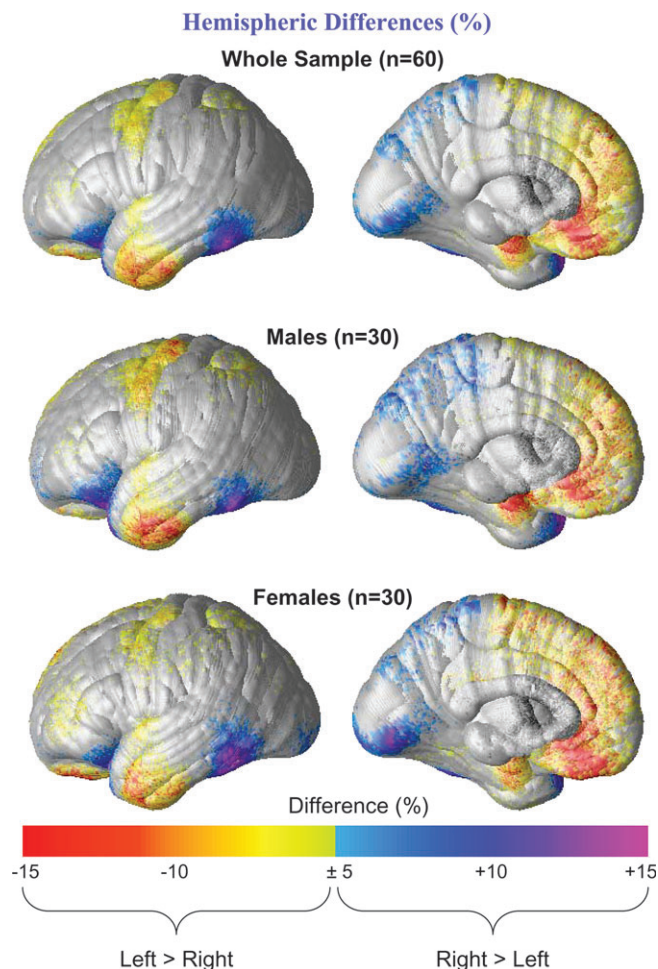
surface models for each hemisphere based on automatically generated spherical mesh surfaces that were continuously deformed to fit a threshold intensity value that best differentiates extracortical CSF from underlying cortical GM (MacDonald *et al.*, 1994). As a result of the linear transformation procedure, the generated 3D cortical surface models correspond globally in size, orientation, and parameter space coordinates. Nevertheless, the same parameter space coordinates within each cortical surface model do not yet index the same anatomy across all subjects and in the left and right hemispheres. Therefore, the cortical surface models from each individual were used to identify and manually outline 16 sulci in each lateral hemisphere as well as 12 sulci in each medial hemisphere, where raters were blind to group status. The outlined lateral sulci included the Sylvian fissure, central, post- and pre-central sulcus, inferior and superior temporal sulcus (main body and ascending branch), inferior and middle frontal sulcus, intraparietal sulcus, transverse occipital sulcus, occipito-temporal sulcus, olfactory and collateral sulcus, as well as the primary and secondary intermediate sulcus, which constitute the posterior borders of the supramarginal and angular gyrus, respectively. The set of medial sulci included the callosal sulcus and inferior callosal outline segment, superior and inferior rostral sulcus, paracentral sulcus, anterior and posterior segments of the cingulate sulcus, outer segment of a double parallel cingulate sulcus (when present), parieto-occipital sulcus, anterior and posterior segments of the calcarine sulcus, as well as the subparietal sulcus. Detailed anatomic protocols for delineating cortical anatomy are available at <http://www.loni.ucla.edu/~esowell/edevl/proto.html>. Since it is not possible to compute intraclass correlations for 3D curves (as these are not simple scalar measures), inter-rater reliability of manual outlining was measured by mapping the 3D root mean square (r.m.s.) difference in millimeters between 100 equidistant points from each sulcal landmark in six test brains that were traced by one rater and compared with a gold standard arrived at by a consensus of raters. Intra-rater reliability was also computed by comparing the 3D r.m.s. distance between equidistant surface points from each sulcal landmark traced six times in one test brain by the same rater. The 3D r.m.s. distance was <2 mm, and on average <1 mm, for all landmarks within the rater and relative to the gold standard. The manually derived sulcal landmarks are then used as anchors to drive the surrounding cortical surface anatomy of each individual into geographic correspondence, where the same cortical surface locations also match point locations in the images that contain the thickness information (Thompson *et al.*, 2004).

### **Statistical Analysis**

We first calculated the mean thickness at each of 65 536 cortical surface points across subjects, and then calculated ratios between local left hemisphere (LH) and right hemisphere (RH) thickness values in order to provide asymmetry maps indicating local hemispheric differences by percentages (Fig. 1). Paired *t*-tests were performed at each cortical surface point to assess the local differences in cortical thickness between LH and RH. Uncorrected two-tailed probability values ( $P < 0.05$ ) from these tests were mapped directly onto the average cortical surface model of the entire sample, providing detailed and spatially accurate maps of hemispheric thickness asymmetries (Fig. 2). However, given that *t*-tests were made at thousands of cortical surface points and adjacent data points are highly correlated, permutation testing was employed to serve as a safeguard against Type I error. For permutation testing, data were randomly assigned to either LH or RH group 100 000 times, and a new statistical test was performed at each cortical surface point for each random assignment. The number of significant results from these randomizations was then compared with the number of significant results in the true assignment to produce a corrected overall significance value for the uncorrected statistical maps. [The number of significant results in the true assignment was determined by calculating the surface area (number of surface points) of significant effects in the real statistical maps. In contrast to calculating the surface area by applying a threshold of  $P = 0.05$  (which was the threshold chosen to color-code the significance maps), we ran the permutation for a stricter threshold of  $P = 0.01$ .]

Finally, for each subject we calculated one global thickness index for each hemisphere by averaging thickness values from all surface points in the respective hemisphere. Paired *t*-tests were applied to compare global thickness indices between LH and RH (Table 1). All statistical





**Figure 1.** Maps of cortical thickness asymmetry as a percentage. Negative values on the color bar (yellow and red) encode a greater thickness in the LH, while positive values (blue and purple) represent greater thickness in the RH. Hemispheric differences  $<5\%$  (regardless of leftward or rightward) are color-coded in gray. Callosal, subcallosal, and midbrain regions have been excluded on the medial aspect of the surface, as the cortex is not present there.

analyses (including permutation testing) were conducted for the whole sample, but also within males and females separately. In addition, we performed supplemental statistical analyses of variance in order to assess potential interactions between gender and hemisphere for regional cortical thickness measurements.

## Results

Figure 1 displays the average distribution of local hemispheric differences in cortical thickness as a percent difference. Note that there is up to a 15% discrepancy between hemispheres. Asymmetry patterns were similar in males and females in lateral and medial cortical regions.

Figure 2 displays statistically significant asymmetries of cortical thickness. Leftward asymmetries appeared to be spread over larger regions than rightward asymmetries. The most significant and extended clusters of leftward asymmetry ( $L > R$ ) were located in the anterior temporal lobe including the inferior, middle and superior temporal gyrus, and in the precentral gyrus extending anteriorly to adjacent regions. Two additional larger clusters favoring the LH were detected in the middle frontal gyrus and superior parietal lobe (extending further down more diffusely, covering the inferior parietal

lobe and supramarginal gyrus). Smaller clusters of leftward asymmetry were observed in superior frontal regions very close to the midline extending along the longitudinal fissure and in the orbital gyrus. Leftward asymmetries on the medial surface were located in anterior parts of the brain (comprising the whole anterior cingulate gyrus and medial frontal gyrus, and surrounding the junction of the temporal and frontal lobes). The patterns of leftward asymmetry are similar in males and females, albeit slightly more pronounced in males for most regions. There is only one region situated in the medial orbital gyrus that seems to possess larger hemispheric differences in females than in males (Fig. 2, left panel).

Distinct clusters of significant rightward asymmetries ( $R > L$ ) were observed on the lateral surface in the posterior inferior temporal lobe; these seemed to be more pronounced in females than in males. In contrast, rightward asymmetries as observed in the cortical thickness of the inferior frontal gyrus (comprising the pars orbitalis, triangularis and opercularis, and extending into the extreme anterior tip of the temporal lobe) appeared to be much larger in male than in female brains. Another smaller region with less pronounced rightward asymmetry was detected near the frontal pole, though this asymmetry was almost undetectable in female brains. Rightward asymmetry in cortical thickness on the medial surface is located posteriorly, comprising the precuneus and lingual gyrus with smaller hemispheric differences in females than in males (Fig. 2, right panel).

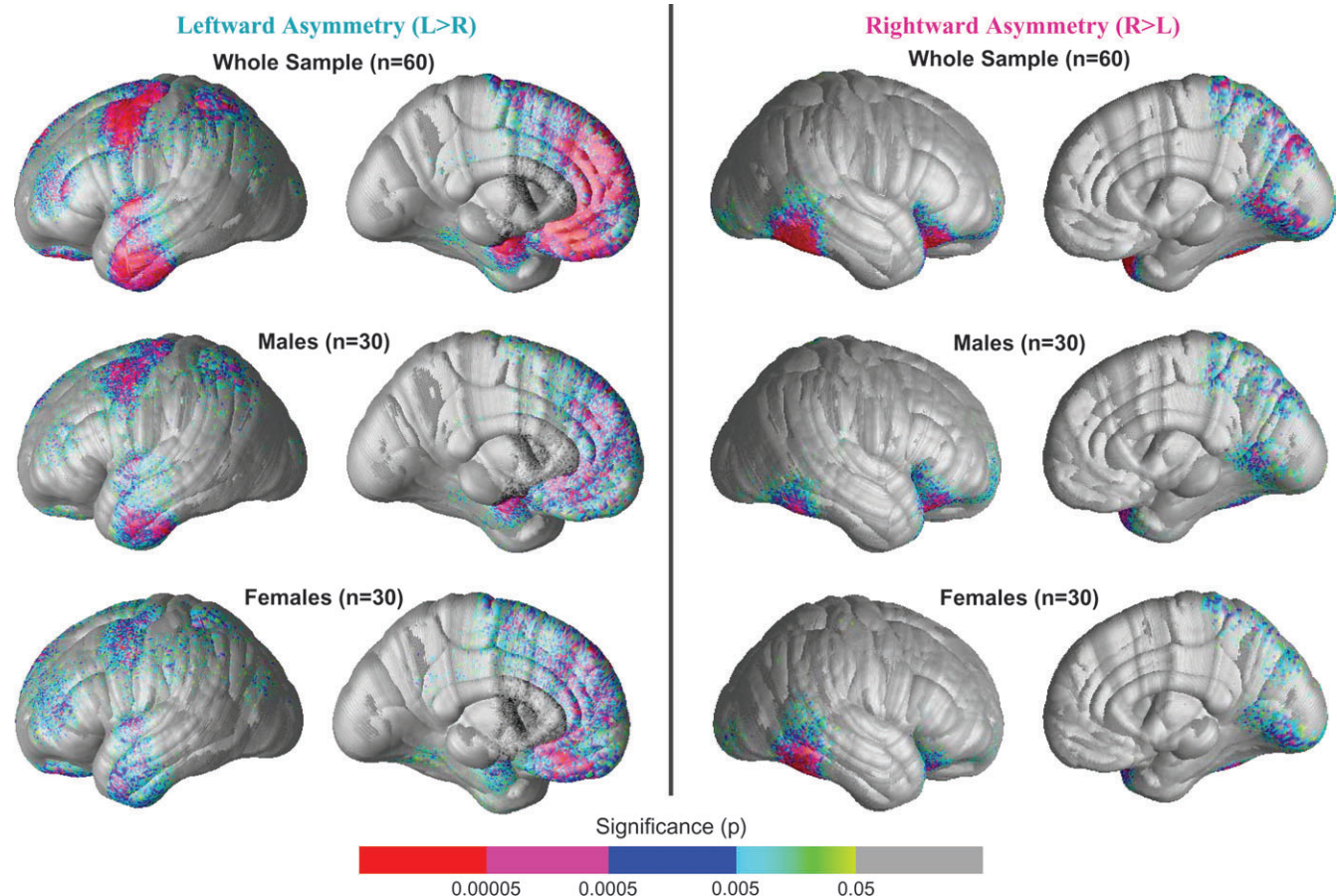
Permutation tests were highly significant for the comparison of thickness between LH and RH for the whole group ( $P < 0.00012$ ), in males ( $P < 0.00049$ ), and in females ( $P < 0.00038$ ), indicating that the observed asymmetry effects do not occur by chance. Although statistical maps in Figure 2 appear to indicate gender differences in cortical thickness asymmetry, supplementary statistical analyses did not reveal significant regional interactions between gender and hemisphere in any cortical region (maps not shown).

Table 1 shows means and standard deviations of global thickness indices averaged across the whole hemisphere. The paired  $t$ -tests revealed a highly significant leftward asymmetry within the entire study group [ $t(1,59) = 11.45$ ,  $P < 0.0001$ ], in males [ $t(1,29) = 5.80$ ,  $P < 0.0001$ ] and in females [ $t(1,29) = 12.43$ ,  $P < 0.0001$ ].

Similarly, counting the number of significantly asymmetric surface points in the whole sample, we revealed pronounced leftward asymmetry ( $n = 16035$ ) compared with rightward asymmetry ( $n = 6646$ ). Interestingly, when asymmetry was plotted for different thresholds of significance (Fig. 3), rightward asymmetry outranged leftward asymmetry for stricter thresholds ( $P < 0.0005$ ) with  $n = 2790$  (rightward) versus  $n = 1037$  (leftward). Nevertheless, the number of significant leftward asymmetric surface points was considerably larger, when counting at significance levels of  $P < 0.005$  and  $P < 0.05$  [ $n = 6420$  (leftward) versus 1380 (rightward); 8578 (leftward) versus 2476 (rightward)].

## Discussion

We used an automated method to measure thickness across the cortex in a well-matched sample of young, healthy adults to investigate hemispheric asymmetries and the influence of gender. We found regionally specific differences between the two hemispheres with more pronounced leftward than rightward asymmetry, and somewhat more pronounced asymmetry



**Figure 2.** Uncorrected maps of significant cortical thickness asymmetry. The color bar encodes the  $P$ -value associated with the  $t$ -tests of cortical thickness performed at each cortical surface point. All colored cortical regions indicate statistically significant differences. All gray-shaded regions are not significantly different between LH and RH.

**Table 1**

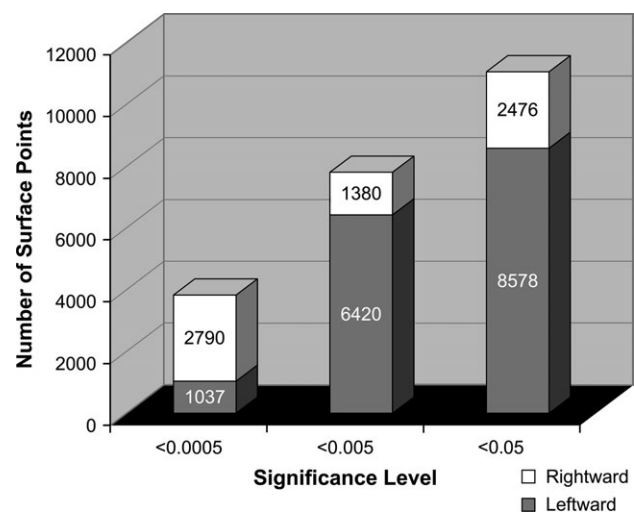
Means and SDs of global thickness indices averaged across the whole hemisphere in standard 305 space

	Whole sample	Males	Females
LH	2.42 (0.14)	2.33 (0.10)	2.51 (0.13)
RH	2.36 (0.13)	2.28 (0.10)	2.43 (0.12)

in males than in females, although asymmetry profiles appeared to be strikingly similar in both sexes.

### Correspondence with Previous Findings

Reports of hemispheric asymmetries in GM indices and/or cytoarchitectonic peculiarities (Niznikiewicz *et al.*, 2000; Good *et al.*, 2001; Watkins *et al.*, 2001; Sowell *et al.*, 2002; Kovalev *et al.*, 2003; Bogolepova and Belograd', 2004; Salat *et al.*, 2004) appear to be in line with our findings of global and regional leftward asymmetries of cortical thickness in the precentral gyrus, anterior superior temporal lobe, superior inferior parietal lobe and medial frontal lobe, as well as rightward thickness asymmetries in the posterior inferior temporal gyrus and inferior frontal lobe. However, we also detected leftward asymmetries in the anterior cingulate gyrus and middle frontal gyrus, contrasting with previous findings of rightward GM asymmetries in those regions as revealed using volumetric and voxel-based measures (Paus *et al.*, 1996; Watkins *et al.*, 2001).



**Figure 3.** Cortical thickness asymmetry in the whole sample. The graph demonstrates leftward and rightward asymmetry in terms of cortical surface points corresponding to significance levels of  $P < 0.0005$ ,  $P < 0.005$  and  $P < 0.05$ , respectively.

Interestingly, the patterns of rightward thickness asymmetry observed in posterior regions on the medial surface of the brain have also not been observed in previous analyses of GM volume or density, but are in close agreement with recent results from



analyses in patients with epilepsy and schizophrenia (unpublished data).

Differences in results between studies conducting GM density and thickness measurements might be attributable to different methodological approaches. Furthermore, although both GM density and thickness measures are directly influenced by signal intensities, the current approach not only takes into consideration the GM value at a given location, but is also based on the regional cortical depths at which voxels are classified as GM. Consequently, corresponding or similar results, in which thickness asymmetry patterns match the profile of hemispheric differences of cortical GM concentration, might be attributable to the shared sources of the different approaches, while deviant findings might result from the unique features inherent to each approach.

Global asymmetry indices clearly indicate an overall leftward asymmetry in both sexes and regional asymmetry patterns that are similar in men and women. Although regional hemispheric differences appear to be slightly pronounced in males compared with females in most regions of the cortex where significant asymmetries were observed, statistical tests revealed no significant interactions between gender and hemisphere. These findings corroborate earlier reports of similar structural asymmetries in men and women (Foundas *et al.*, 1999; Watkins *et al.*, 2001), albeit contrasting with findings of greater structural asymmetry in men (Jancke *et al.*, 1994; Kulynych *et al.*, 1994; Frederikse *et al.*, 1999; Gur *et al.*, 1999; Shapleske *et al.*, 1999; Amunts *et al.*, 2000; Good *et al.*, 2001). Nevertheless, previous analyses have never been conducted to establish hemispheric differences in cortical thickness but rather with respect to area, sulcal depths, GM volume and percentage.

### Functional Implications

Since the MRI signal strength and thus the measurement of cortical thickness is related to cellular characteristics such as cell packing density, myelination, cell size and number of cortical neurons (Kruggel *et al.*, 2003; Eickhoff *et al.*, 2004), thickness asymmetries of the cortex might be related to hemisphere-specific functional specializations. For example, since we exclusively analyzed brains of right-handers, the pronounced leftward asymmetry in the superior precentral gyrus might be associated with the dominance of the LH for motor functions of the right hand. Similarly, structural correlates of handedness in the sensorimotor system have been suggested previously and are supported by findings reflecting morphological asymmetries in the cortico-spinal tract (Yakovlev and Rakic, 1966; Melsbach *et al.*, 1996) and macrostructural or microstructural asymmetries in regions in or adjacent to the primary motor cortex (White *et al.*, 1994; Amunts *et al.*, 1996, 2000; Davatzikos and Bryan, 2002). However, if such a direct relationship between cortical thickness and functional lateralization always existed, we would expect striking leftward asymmetries for cortical regions supporting language functions, given that the LH is known to be specialized in speech and language comprehension (Price, 2000). Although we detected leftward asymmetry in some regions that process language and speech (superior temporal gyrus, supramarginal gyrus), regions near primary anterior language regions showed a pronounced rightward asymmetry, contrasting prior findings where leftward asymmetries were detected (Galaburda, 1980; Falzi *et al.*, 1982; Albanese *et al.*, 1989; Foundas *et al.*, 1996, 1998). This notwithstanding, those previous results are based on post

mortem and/or ROI analyses (rather than automated whole brain approaches), so that methodological differences could account for divergent asymmetry findings. Moreover, prior reports of leftward asymmetry are based on measurements of area sizes rather than on measurements of cortical GM or thickness, clearly capturing a different aspect of brain anatomy. Interestingly, with respect to the latter mentioned measurements of interest (GM concentration), rightward asymmetries and/or absent leftward asymmetries in anterior language areas have been demonstrated (Sowell *et al.*, 2002; Watkins *et al.*, 2001) and corroborate our present findings. Hence, it is arguable that there is only a one-dimensional and unidirectional link between the asymmetry of cortical thickness at a particular cortical location and the functional organization and degree of hemispheric specialization of this region. Consequently, we would abstain from prematurely interpreting the possible functional or behavioral correlates of our observed thickness asymmetries.

### Future Analyses

Investigating the relationship between the asymmetry of cortical thickness and functional lateralization will be an important goal for future studies. In addition, our asymmetry findings might be used to direct more focused and detailed analyses of thickness asymmetry through conventional ROI analyses or other brain mapping approaches. For example, the overall profile of thickness asymmetry that exhibited within the medial wall is intriguing given that the predominant leftward asymmetry (in anterior medial brain regions) reverses in the vicinity of the paracentral gyrus into a rightward asymmetry (in posterior medial brain regions). Differences in hemispheric morphology have been suggested to originate from a complex interplay between evolutionary, hereditary, developmental, experimental, and pathological factors (Toga and Thompson, 2003). Thus, our findings might not only serve as reference data from a large, well-matched sample of young adults against which future findings of cerebral asymmetries in healthy subjects and neuropsychiatric or neurodegenerative patients can be compared, but also as source to generate new hypotheses. Finally, our results could be relevant for studies using functional MRI (fMRI). It had been demonstrated that the blood oxygenation level-dependent contrast can depend on the thickness of the cortex (Rasser *et al.*, 2005). Therefore, the asymmetry of cortical thickness may influence differences of fMRI activation between the hemispheres.

### Potential Limitations

Brain volumes were automatically segmented by classifying voxels into GM, WM, CSF or background. Such automated techniques are problematic because of the regionally variable contrast of the cortex-WM border. MRI-based segmentation of the cortical ribbon does not always reflect the neuroanatomical definition of the cortical ribbon. In histological specimens stained for cell bodies, the cortex-WM transition is often not easily delineable, since the decrease of neuronal density towards the WM is not abrupt, but rather gradual in many cortical regions. In addition, this degree of ambiguity varies not only across cortical areas but also depending on the local degree of cortical folding. At the crown of a gyrus, lower layers appear to be more dispersed, which results in a blurred cortex-WM transition. MRI based, automated voxel classification often fails to deal with this problem. However, we used well-validated

tissue segmentation algorithms (Shattuck *et al.*, 2001). Moreover, different studies using independent samples in our laboratory (Narr *et al.*, 2004; Sowell *et al.*, 2004) applying the same thickness approach, have revealed spatial distributions of cortical thickness that agree with those revealed through post-mortem analysis by von Economo (1929). However, it appears to be less clear, how thickness measurements may relate to other biological measures obtained from imaging (e.g. volume and density of cortical GM). For example, a study by Wiegand *et al.* (2004) showed significant relationships between GM volumes and cortical thickness measured exclusively in the frontal cortex, while Narr *et al.* (2004) showed highly significant relationships between GM density and thickness over the majority of the cortical mantle.

Comparing LH and RH cortical thickness, we revealed a surfeit of leftward asymmetry that was clear in both regional and global asymmetry measurements in men and women. One potential confound is that any residual magnetic field inhomogeneities, not explicitly corrected by bias field correction, could lead to signal intensities distributed unevenly between the hemispheres. However, since we used a 1.5 T whole-body scanner for the acquisition of the data, field inhomogeneities are minor in general and would be corrected by the explicit correction for RF inhomogeneity. Also, any RF inhomogeneities tend to be of low spatial frequency, and they are generally a small magnitude multiplicative field, with values near 1, so they would be expected to shift both boundaries of the cortical GM roughly equally, if at all. As a result, it is extremely unlikely that inhomogeneities account for the observed asymmetries. Thus, hemispheric differences in cortical thickness seem to reflect neurobiological differences than a neuroimaging artifact.

Finally, hand preference and hand performance may affect regional measures of thickness asymmetry. It has frequently been reported that handedness is correlated with different measures of brain asymmetry (Jancke *et al.*, 1994; Steinmetz *et al.*, 1991; White *et al.*, 1994). Given that subjects of the present study were selected based on self-reports of right-handedness without discriminating between different degrees of handedness, it is possible that asymmetry effects might have been even more pronounced in a sample of only strong right-handers. Future analyses might profit from classifying subjects based on standardized handedness inventories and/or performance measurements and reveal additional insights.

## Notes

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